CHAPTER 48 – Bioresearch Monitoring

SUBJECT:	IMPLEMENTATION DATE
RADIOACTIVE DRUG RESEARCH COMMITTEES	December 1, 2012
	COMPLETION DATE
	December 1, 2015

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for Bioresearch Monitoring Inspections	48809A Radioactive Drugs for Human Use

FIELD REPORTING REQUIREMENTS:

Copies of all establishment inspection reports (EIRs) complete with attachments, exhibits, and any related correspondence are to be submitted promptly to the Center (usually the reviewer in the Center's Bioresearch Monitoring (BIMO) program identified in the assignment).

All EIRs should be completed in accordance with FMD No. 86, Establishment Inspection Report (EIR) - Inspection Conclusions and District Decisions and the Investigations Operation Manual (IOM), Chapter 5, Establishment Inspections. When a FDA Form 483, "Inspectional Observations" (483), is issued, a copy should be forwarded to the Center contact (by facsimile or e-mail, or filed in a shared folder, as agreed to with the Center), as soon as possible, generally within 3 business days after being issued.

PART I - BACKGROUND

A. GENERAL

Under 21 CFR 361.1, human research using a radioactive drug or biological product may be conducted without an Investigational New Drug (IND) application under an FDA approved Radioactive Drug Research Committee (RDRC), but only when that research is basic science research, and not research that is intended for immediate therapeutic, diagnostic, or similar purposes, or to determine the safety and effectiveness of the radioactive drug or biological product for such purposes. Such research cannot be considered a clinical trial for the product.

B. AUTHORITY AND PROCEDURES

The Federal Register of July 25, 1975, includes a final order establishing regulations, which specify the conditions under which radioactive drugs for certain research uses, other than clinical trials for safety and efficacy, are not subject to the new drug requirements of the Federal Food, Drug and Cosmetic Act as amended.

Radioactive drug is defined in 21 CFR Section 310.3(n):

> *The term "radioactive drug" means any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace amounts of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in section 600.3(ee) of this chapter.*

To be exempt from the requirements of the new drug regulations, radioactive drugs intended for basic research in humans must meet the requirements of 21 CFR 361.1. This section provides exemptions for radioactive drugs used in research that are approved and monitored by a Radioactive Drug Research Committee. Section 361.1 specifies the criteria for the performance of such a committee.

An additional regulation has been promulgated at 21 CFR 201.129, which provides an exemption from section 502(f)(1) (adequate directions for use) of the Federal Food, Drug, and Cosmetic Act if the packaging, labels, and labeling of the research drugs are in compliance with section 361.1(f) of FDA regulations.

PART II - IMPLEMENTATION

A. OBJECTIVE

The objective of this program is to determine whether Radioactive Drug Research Committees (RDRCs) are operating in compliance with 21 CFR 361.1. In addition, the objective of the program is to ensure that FDA meets its requirement to monitor the activities of RDRCs by conducting on-site inspections as required by 21 CFR 361.1(c)(5). Any RDRC that is determined to be seriously out of compliance with the regulations may have its approval withdrawn as described in 21 CFR 361.1(c)(4).

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. Coverage -- This program provides for the inspection of all RDRCs. These FDA approved committees review and approve certain research uses of radioactive drugs that are generally recognized as safe and effective (GRASE). These radioactive drugs must be administered under the conditions set forth in 21 CFR 361.1(b), primarily (1) the study must be approved by the RDRC, (2) the RDRC must assure that the amount of active ingredient administered causes no clinically detectable pharmacological effect and (3) that the subjects receive the smallest practical radiation dose to do the study without jeopardizing the benefits to be obtained from the study.

2. Due Dates -- All assignments will be issued by the Center for Drug Evaluation and Research (CDER), Office of Scientific Investigations (OSI) and will have a ninety (90) day completion date unless otherwise indicated.

C. OPERATIONS

Each inspection should include a comparison of the practices and procedures of the RDRC with the requirements of 21 CFR 361.1.

RDRC inspection assignment memorandums will be issued by CDER/OSI in consultation with the Division of Medical Imaging Products (DMIP). Assignments will be issued both on a routine and for cause basis.

The Office of Regulatory Affairs (ORA) field investigators will conduct the inspections of RDRCs and will complete an establishment inspection report at the conclusion of each inspection. If, during an inspection attempt, the field investigator determines that the FDA lacks jurisdiction over the site (i.e., the RDRC has dissolved, the RDRC is not currently monitoring research, etc.), the inspection will be completed as per the directions in the IOM. A copy of the memorandum will be promptly submitted to the Center.

When scheduling the inspection, the FDA investigator will contact both the administrator of the institution and the chairman of the RDRC. An individual contact person for the site visit should be identified, and the time interval between the notification and the inspection should be as short

as possible.

Each district will assign a Field Establishment Inspection (FEI) number for RDRCs located within their district. Districts will be responsible for maintaining the individual RDRC operational status in the database.

The "Institutional Review Board" compliance program is different and does not include coverage of the Radioactive Drug Research Committees (RDRCs). Requesting and assessing inspections of RDRCs are the responsibility of CDER/OSI, after consultation with the Division of Medical Imaging Products/Office of Drug Evaluation (ODE) IV. Issuing inspection request assignments which include both an IRB and a RDRC will be the responsibility of CDER/OSI.

1. Inspection Assignments

   a. CDER/OSI issues inspection assignments of RDRC sites.

   b. To ensure the appropriate and efficient use of FDA resources, RDRC assignments will follow FMD No. 17, ORA Field Assignments - Guidelines for Issuance by Headquarters, whether from an ORA headquarters unit or a Center.

   c. The assignment should identify:

      - The program assignment code (PAC) and Field Accomplishments and Compliance Tracking System (FACTS) number, Firm Establishment Identification (FEI) number, if known;
      - The name, address and phone number of the RDRC, when available, to be inspected;
      - The type and purpose of the inspection (e.g., routine inspection (surveillance), directed inspection (complaint, OAI follow-up, For Cause));
      - The background materials that are being sent from the Center to facilitate the inspection (e.g., annual reports);
      - Specific issues or concerns (if applicable) that need to be addressed during the inspection;
      - The due date for the Center contact to receive the completed EIR;
      - The headquarters address where the EIR should be sent; and
      - The name, telephone number, and fax number of the Center contact(s).

   d. Inspection of the Department of Veterans Affairs (VA) as the RDRC of FDA-regulated clinical trials.

      (ii) Pre-Inspection

      - **Center**. The BIMO unit in the assigning Center will provide the VA's office of Research Oversight (ORO) with written notification of FDA's intention to

inspect a VA RDRC program at the time an assignment is being issued to the field. The notice should be sent to:

Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

- **Field**. The field investigator will contact the VA RDRC program described in the assignment prior to the inspection, as they would any other RDRC they are assigned to inspect. Contact information for the VA RDRC will be provided in the assignment.

(iii) Post-Inspection

- **Center**. The Center will provide the VA's ORO redacted copies of post-inspection correspondence issued to VA RDRC programs that include a discussion of deficiencies noted during the inspection (including the FDA-483s). Such materials should be sent to:

Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

- **Field**. If, following receipt of the FDA correspondence, the VA-ORO requests a copy of the EIR, a redacted copy of the report will be provided to VA-ORO by the District office.

e. All headquarters and field personnel who become aware of complaints or problems related to an RDRC are encouraged to refer them to the CDER/OSI contact with a recommendation for inspection. All recommendations should include the following:

- The name and address of the RDRC;
- If available, the name(s) of the test article(s) being investigated; and
- The basis for the recommendation and any relevant documentation.

2. Communication between the Centers and the Districts

Inspectional observations documenting that an RDRC is not operating in compliance with the regulations in 21 CFR Part 361.1 may be used as evidence for taking appropriate administrative and/or enforcement actions. Ensuring that the evidence collected to support such actions is both appropriate and adequate requires that

communication lines between the ORA District office and the Center be established early and maintained throughout the entire process, i.e., until post-inspectional correspondence is issued by the Center. Contact between a Center and an ORA field investigator will respect that District's policy for direct contact between field investigators and Center personnel and may require ORA management participation.

a. Prior to an Inspection

- The Center issues an assignment that includes contact information for the BIMO reviewer.
- The field investigator contacts the BIMO reviewer:
  - Upon receipt of the assignment, to establish initial contact and/or provide an inspection start date;
  - When the inspection date is firmly set, to alert the BIMO reviewer and/or a back-up to be available and to establish the most appropriate means of contact for both the investigator and the BIMO reviewer/back-up;
  - To obtain any new information that may change the focus of the inspection; and
  - To coordinate inspection arrangements if Center personnel plan to participate in the inspection.

b. Special Considerations

- In particular cases, the Center may arrange for a consultative teleconference immediately prior to the inspection(s) if, for example, the complexity of issues, urgency of feedback, compliance history, etc., trigger the need to discuss issues further. Such conference calls are most likely when the agency encounters special situations (e.g., "directed" inspections where pertinent information is either complex or needs discussion between the Center and the field). Unless information necessitating this discussion emerges after the assignment is issued, the assignment will usually include information as to when this teleconference will occur.
- These teleconferences may include the following participants, as warranted and feasible:
  - BIMO reviewer (and supervisor/division director or other staff, as appropriate);
  - DMIP reviewer (along with branch and division chiefs, if appropriate);
  - Field investigator(s) assigned to the inspection(s), the BIMO coordinator (when not yet specifically assigned), and ORA management and staff, as appropriate.

c. During an Inspection

- The BIMO reviewer contacts the field investigator if significant new information becomes available.
- The field investigator contacts the BIMO reviewer or designated back-up person if the field investigator:
  - needs advice or clarification. The BIMO reviewer and field investigator should strive to be accessible to one another as much as possible during the time that the inspection is ongoing.
  - uncovers other evidence of concern warranting discussion with Center staff.

d. After an Inspection

- As soon as possible but within three (3) business days after conclusion of the inspection, the field investigator forwards to the BIMO reviewer (by facsimile, e-mail, or placement in the appropriate shared drive folder) any 483 that is issued.
- The field Investigator/District will forward as soon as possible to the BIMO reviewer a copy of any written response to the 483 by the inspected party. The BIMO reviewer will forward to the field investigator, a copy of any response to a 483 that does not appear to have been shared with the inspecting District. If desirable, the field investigator provides Center contact information so that the response to the 483 can be sent directly to the Center for review in addition to sending it to the field inspector/District Office.
- For general guidance for handling unsolicited responses resulting from the issuance of the 483, please see Field Management Directive #120.
- The BIMO reviewer consults with the field investigator/District representative as needed when reviewing the EIR.
- When applicable, the Center consults with appropriate District personnel if contemplating an EIR classification different from the one recommended by the District.
- If the Center's final classification is different from the one recommended by the field, the Center will discuss the re-classification with District personnel to ensure they are aware of the change and reasons for the change.
- The Center promptly forwards to the field investigator and other appropriate District personnel by e-mail, if possible, copies of post-inspectional correspondence issued to the inspected party.
- The Center enters the final classification into FACTS.

3. Responsibilities of Field Investigators, Inspection Team Leaders, and Headquarters

Participants

a. When conducting solo inspections

When conducting solo inspections, the field investigators responsibilities include, but are not limited to, the following:

- Scheduling and conducting the assigned inspection;
- Communicating inspectional observations with the institutional officials and RDRC staff during the course of the inspection, as appropriate;
- Communicating inspectional observations and issues with the Center contact during the course of the inspection and review, as appropriate;
- Preparing, issuing, and discussing the items listed on the 483 with the RDRC at the close of the inspection;
- Preparing and submitting an establishment inspection report (EIR) within FDA timelines; and
- When appropriate and if time allows, participating in discussions with the Center regarding potential changes in the EIR classification.

b. When conducting team inspections

When inspections are conducted by a team, a field investigator serves as inspection Team Leader who is responsible for the cooperative conduct of the inspection. The Team Leader's responsibilities include, but are not limited to the following (see also IOM, Chapter 5, section 5.1.2.5 - Team Inspections):

- Scheduling and coordinating the participation of team members;
- Discussing inspection plans and objectives with team members;
    - Assuring that team members understand their roles and responsibilities in conducting the inspection, taking notes, collecting documentation, preparing sections of the inspection report and exhibits, and signing the report;
- Setting team policy regarding communications with institutional officials and/or the RDRC staff;
- Discussing personal conduct with team members as necessary; and
- Resolving disputes or differences of opinion among team members, including items to be listed on the 483. If an agreement cannot be reached during the inspection, the final items included on a 483 will be decided by the ORA field investigator.

c. Headquarters Participants

A headquarters participant is a member of the inspection team who serves in a

compliance or scientific advisory capacity to the Team Leader. The headquarters participant's responsibilities include, but are not limited to, the following:

- Obtaining training on inspection conduct and behavior prior to participating in inspections;
- Obtaining inspection credentials from the Division of Domestic Field Investigations (DDFI) (HFC-130);
- Completing the Inspection Participation Form (Form FDA 2115);
- Contacting the Office of Regional Operations (ORO) to request permission to participate in field inspections;
- Providing information pertinent to the inspection;
- Attending pre-inspection discussions, if and when requested by the Team Leader;
- Participating in the on-site inspection as permitted by agency priorities; and
- Providing technical guidance and expertise during the inspection and completing inspection tasks as directed by the Team Leader (e.g., auditing documents, preparing inspection notes and specific sections of the establishment inspection report within guidelines and timeframes).

4. Resolution of Disagreements

If there is disagreement among members of the inspection team, the issue should be discussed off-site and resolved cooperatively. Any difficulties in conducting team inspections should be discussed with both District management and the assigning Center, and, if not resolved, immediately referred to the Division of Domestic Field Investigations (DDFI) (HFC-130).

PART III – INSPECTIONAL

A. OPERATIONS

The goal of the RDRC inspection program is to assess an RDRC's current operations. An individual RDRC may be responsible for reviewing and approving many research studies. CDER/OSI will provide a listing of studies for audit selection. The selected studies should represent research protocols that may suggest potential problems or possible violations of the RDRC regulations (21 CFR 361.1). In the case of a for-cause inspection, such specific assignments will usually be accompanied by specific instructions, which would be in addition to this compliance program.

In selecting studies for review, and collecting exhibits, the following points should be kept in mind:

1. Section 361.1 may not apply to all radioactive drugs at the institution, therefore the investigator must be careful to differentiate RDRC radioactive drugs with those that are not regulated under 21 CFR 361.1(a), such as approved radioactive drugs or those under an IND.

2. An informed consent document must be evaluated with the study's protocol. Therefore, EIR exhibits should contain both the study protocols and associated informed consent documents.

B. REPORTING

1. The Districts are responsible for conducting inspections and preparing EIRs. All reports, including copies of exhibits, are to be submitted directly to the Center initiating the assignment. CDER personnel participating in the inspection will be responsible for preparing those sections of the EIR pertaining to areas he/she covered during the inspection, as discussed in section II of the compliance program.

2. The EIR should contain the headings as prescribed in the IOM. Centers encourage submitting electronic inspectional documents, if possible. Any adverse findings should be fully explained and documented in the EIR.

3. The EIR should address each question listed under Section III G. below.

4. A 483 should be issued under this program when deviations from the requirements in 21 CFR Part 361.1 are observed.

NOTE: Reports must include the name and address of the RDRC Chairperson and should include the name and address of the head of the institution at which the RDRC is located.

5. For No Action Indicated (NAI) inspections, please follow the guidelines outlined in the inspection assignment for collecting records and documents.

6. Please remember to collect records and documents related to all 483 observations to support the violations noted on the form.

C. ESTABLISHMENT INSPECTIONS

The inspections should be guided by the regulations found in 21 CFR Part 361.1.

D. PRIOR NOTIFICATION OF INTENT TO INSPECT

1. General

   To assure that responsible individuals are present and that RDRC records are available, the FDA field investigator shall contact the institution to confirm the name and location of the RDRC Chairperson to schedule the inspection. The primary purpose of such prior notice is efficient use of the field investigator's time.

2. District management may elect to conduct unannounced inspections with approval of the assigning Center, if conditions warrant.

E. REFUSAL TO INSPECT

If the institution refuses to permit either the inspection, access to records, or copying of records, or if delays instituted by the inspected firm are such that they constitute a de facto refusal, inform your supervisor so he/she can advise the assigning Center promptly by telephone. Send a follow-up e-mail to the listed Center (per the assignment) and ORA contacts specified in Part VI B.2. "Program Contacts". IOM 5.2.5 – Inspection Refusal provides additional guidelines.

F. SUBSEQUENT RELATED SPONSOR/INVESTIGATOR INSPECTIONS

An RDRC inspection may reveal significant regulatory deviations which may lead to sponsor/investigator inspections. Districts may carry out such inspections after obtaining the necessary instructions from the appropriate Center. The Center may issue these assignments as directed inspections.

G. INSPECTION PROCEDURES

1. The field investigator shall determine whether the Radioactive Drug Research Committee has met the criteria of 21 CFR 361.1 by asking the following questions. Additional information is also available in the Inspection Operations Manual:

   a. Do records show that the RDRC is composed of members who meet the requirements

of the regulations? [section 361.1(c)(1)]

b. Do records show that FDA has been notified of current members and changes in committee members? If so, was this done as soon as or before there were changes [as required by 361.1(c)(4)], or did they wait to submit changes with required annual report? Compare attendees listed in minutes of meetings to current Form FDA 2914. Include as an exhibit the most recent membership roster showing members' names and qualifications. Previous membership rosters should be collected as needed.

c. Does the committee meet at least once each quarter in which research activity has been authorized or conducted? [section 361.1(c)(2)]. If a study has been authorized by the RDRC and is considered "open" or "active" in the records of the RDRC, but no subjects were accrued during that calendar quarter, there is an expectation from FDA that the committee should meet (requiring a quorum with representation from each of the required membership categories) at least to report within the meeting minutes of the committee, the business that was discussed with the quorum members and the status of the studies and any old or new business before the committee.

d. Is there documentation that the RDRC does quarterly reviews? Describe how the committee monitors and documents the progress of each study. [section 361.1(c)(2)].

e. Does the RDRC give final approval for proposed research only at convened meetings? [section 361.1(c)(2)]

f. Does each committee meeting have quorum of more than 50% of the membership present? Did that quorum include the required nuclear medicine physician, radioactive drug formulator, and a person with competence in radiation safety and dosimetry? [section 361.1(c)(2)]

g. Does the chairman sign the application, minutes, and reports? [section 361.1(c)(2)].

2. Are committee minutes kept, and do they include the numerical results of votes on protocols involving use in human subjects? [section 361.1(c)(2)]. Exhibits should include copies of minutes that document the approval of the selected protocols.

3. Obtain complete copies of relevant materials that document current RDRC performance over the past two years, including meeting minutes and protocols with approved informed consent documents related to RDRC review and approval of protocols tracked through the RDRC review process during the inspection.

4. Are committee members precluded from voting on protocols for which they are investigators? Do meeting minutes accurately document the numerical results of votes on protocols involving use in human subjects? [section 361.1(c)(2)]

5. Has the committee submitted its annual report to FDA on or before January 31 of each

year? Does this annual report cover the previous calendar year? [section 361.1(c)(3)].

6. Has the committee reported immediately (no later than 7 calendar days) to FDA all approved protocols involving more than 30 subjects or any subject under 18 years of age (Form FDA 2915 and a justification statement)? [section 361.1(c)(3)]

7. Are studies involving research subjects under 18 years of age supported with review by qualified pediatric consultants to the committee? Is the pediatric consultant listed on the FDA Form 2914 Membership Summary? [section 361.1(d)(5)]

8. Have any adverse reactions been reported to the RDRC? [section 361.1(d)(8)] If so, have those reactions determined to be probably attributable to the use of the radioactive drug been reported immediately to FDA? [section 361.1(d)(8)].

9. Did the committee determine that the labeling of the research drug complied with section 361.1(f)? (If there is an example of the labeling available, provide a copy as an exhibit.) Do the protocol records include an example of the product vial label?

10. How does the committee consider and assure that the requirements for the quality of the radioactive drug are met? [section 361.1(d)(6)] (For example, is there a list of tests to be performed in the study protocol or the batch record?) Does the RDRC have documentation of the results of product quality tests? Do they review the results of pyrogen and sterility tests performed on the drug products they authorize?

    - Due to the time delay for sterility and pyrogen testing, certain radioactive drugs utilizing short lived isotopes (e.g., F18 - t1/2 = 110 min, Tc99m - t1/2 = 6.02 hours, I124 - t1/2 = 4.2 days, I131 - t1/2 = 8.04 days) cannot wait for such testing prior to release, as radioactivity levels will have diminished beyond useful levels. Sterility and pyrogen testing may be appropriate for other intermediate or long lived isotopes (e.g., I125 - t1/2 = 60 days, H3 - t1/2 = 12.3 years, C14 - t1/2 = 5,730 years). Field investigators should focus their inspection on the extent to which the RDRC requires, and the frequency in which it reviews results of sterility and pyrogen tests for studies it has approved.

11. Is there documentation that the RDRC assured that the investigator obtained the consent of the subjects or their legally authorized representatives in accordance with 21 CFR part 50? Does the informed consent document inform the research subject that they will be exposed to radiation for research purposes which has no direct benefit to them? [section 361.1(d)(5)]

12. Is there documentation that the RDRC assured that the study was reviewed and approved by the Institutional Review Board, consistent with 21 CFR part 56? [section 361.1(d)(5)]

13. Is there documentation that the RDRC assured that each investigator is qualified by training and experience to conduct the proposed research studies? [section 361.1(d)(3)]

14. Is there documentation that the RDRC assured that the investigator or institution is licensed to possess and use radionuclides? [section 361.1(d)(4)]

15. Are RDRC approved studies or protocols limited to basic science research, as specified in 21 CFR 361.1, i.e. they cannot be intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial)? [section 361.1(b)]

    a. For any protocols for which the answer to question 15 is no, are the protocols being conducted under an IND? (If this information cannot be determined at the site, contact the Center representative listed on the assignment to discuss further.)

        (i) For those radioactive drug protocols covered by an IND, the field investigator should assess whether the RDRC chairman (or institutional representative) is aware that FDA does not require review and approval of non-RDRC studies by the RDRC, and the RDRC does not need to report these activities to the FDA.

        (ii) Some institutions use RDRCs for additional radiation safety responsibilities, and reviews of INDs using radioactive drugs. In such cases, meeting minutes should separate RDRC business from other committee responsibilities. This may best be achieved by having separate and distinct RDRC meeting minutes.

    b. Whenever possible, a protocol satisfying the criteria of section 361.1(a) should be included in the EIR to provide the necessary basis for evaluating the review and approval procedures of the RDRC under these regulations.

    c. If a certain study is not covered by an IND and it appears that an IND may have been required, immediately notify the Center representative listed on the assignment, who in consultation with the Division of Medical Imaging Products will determine if an IND is needed.

16. Does the RDRC determine that the pharmacological dose is within the limits set forth in section 361.1(b)(2).

17. Does the RDRC require radiation doses to be calculated for each of the required areas listed in section 361.1(b)(3)(i)? (whole body, active blood-forming organs, lens of the eye, and gonads).

18. For those studies which involve the use of a radioactive drug claimed to be used under the intentions of basic science research as outlined in 361.1(a), but is being used in conjunction with a non-radioactive drug being investigated under an IND, is there evidence that the RDRC assured the study investigator has submitted a summary of results for the outcomes of the RDRC study in the required yearly summary report for the IND?

[section 361.1(e)]

H. ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

Computerized systems are more commonly being used by institutions to collect and preserve records.

Computerized systems range from a desktop or lap top personal computer using an internal network to different systems located at multiple sites which use an Internet connection (e.g., a Web-based system managed by an independent software vendor to which the RDRC, the sponsor and clinical sites have controlled access).

Regardless of the type of system used by the RDRC, an important principle to understand when evaluating RDRC records is that the regulatory requirements for adequate documentation of RDRC activities do not change whether the documentation is captured on paper, electronically, or using a hybrid approach.

21 CFR Part 11 (Part 11) describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 is a companion regulation to other FDA regulations and laws. It is within these other regulations and laws, called predicate rules, where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed.

1. Scope of Electronic Records/Electronic Signatures as Described in Guidance

   a. Section III. B. 2 of the Part 11 guidance document (page 5) states that Part 11 is applicable to the following electronic records and electronic signatures:

   b. Records that are required to be maintained under the predicate rules and that are maintained in electronic format in place of paper format.

   c. Records that are required to be maintained under the predicate rules, that are maintained in electronic format in addition to paper format, and are relied on to perform regulated activities.

   d. Records that are required to be submitted to FDA under predicate rules that are in electronic format.

   e. Electronic signatures that are intended to be the equivalent of handwritten signatures, initials or other general signings that are required by the predicate rules and/or the RDRC's written procedures (if applicable).

      In Section III. C. of the Part 11 guidance document (page 6), specific requirements for which the agency intends to exercise enforcement discretion include the:

- validation of computerized systems;
- use of computer-generated, time-stamped audit trails;
- use of legacy systems;
- generation of copies of records; and
- protection of records (i.e., record retention and availability; see Guidance: General Principles of Software Validation).

2. Inspectional Guidelines

   The field investigator should consult with an ORA management and/or ORA computer national expert for guidance regarding Part 11.

3. Equipment, Procedures, Processes

   Find and document the following:

   a. **Describe** any computerized system(s) used at the RDRC site(s) to generate, collect, or preserve documented RDRC activities (e.g., stand alone personal computer, Web-based system, hand-held computers).

   b. **Determine** whether electronic records or reports are defined in the RDRC's written procedures (if applicable).

   c. **Explain** how the RDRC determines which records (e.g., meeting minutes, voting logs, etc.) are collected and stored in electronic format (i.e., does the RDRC prescribe any off-the-shelf program or follow any written procedures which describe selection of records for electronic formatting).

   d. **Determine** whether electronic records are available for inspection.

   e. **Determine** whether the RDRC's electronic system has operating instructions, user-manuals, access policies and procedures, training policies, or management controls to create, modify, maintain, or transmit electronic records.

   f. **Determine** whether individuals who develop, maintain or use the computerized systems have the necessary training to perform their assigned tasks.

4. Maintenance of Electronic Records

   Find and document the following:

   a. **Determine** whether the RDRC is able to ensure adequate electronic and human readable copies of electronic records suitable for review and copying. (If you are

unable to gain access to records from the computerized system following the procedures outline IOM 5.3 – Evidence Development, contact the Center immediately).

NOTE: Follow IOM 5.3.8.3.2 - Electronic Information Received on CD-R or Other Electronic Storage Media. It states, "Do not personally access a firm's electronic records, databases, or source/raw data during the course of the inspection."

b. **Determine** whether electronic records and documentation meet the requirements applicable to RDRC records maintained in paper format.

c. **Describe** how records, reports, or correspondence are transmitted from the RDRC to the sponsor, clinical investigator, institutional official, FDA, etc., and vice-versa.

d. **Determine** how the computerized system allows changes to be made (e.g., is it based on individual access privileges? Are all changes to electronic source data accompanied with write-protected audit trails to include the name, date, and reason for change?).

5. Security

Find and document the following:

a. **Determine** who is authorized to access the system.

b. **Describe** how the computerized systems are accessed (e.g., password protected, access privileges, user identification).

c. **Determine** how information is captured related to the creation, modification, or deletion of electronic records (e.g., audit trails, date/time stamps).

d. **Describe** whether there is a backup, disaster recovery, and/or contingency plan to protect against record loss. Were there any installed software upgrades, security or performance patches, or new instrumentation that affected the electronic records?

e. **Describe** how error messages or system failures are reported to the RDRC, including the corrective actions taken, if any.

PART IV - ANALYTICAL

No analytical activities are planned under this program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. ADMINISTRATIVE GUIDANCE

1. District EIR Classification Authority

   The District must follow the procedures for assigning District Office inspection conclusions and decisions to an Establishment Inspection Report (EIR) within established timeframes as defined in Field Management Directive, Establishment Inspection Report Conclusions and Decisions (FMD #86).

2. Center EIR Classification Authority

   The Center has final classification authority for all EIRs generated under this compliance program. If the Center is considering a classification that differs from the District's recommended classification, the Center will contact the District to discuss the issues as soon as possible to avoid delays in the final classification process. In addition, the Center will provide the District with notice of all final classifications, including the rationale for any that differ from the District's initial classification.

3. EIR Classifications

   The following guidance is to be used in conjunction with the instructions in FMD-86 for initial District and Center classification of EIRs generated under this Compliance Program:

   a. NAI - No Action Indicated -- No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);

   b. VAI - Voluntary Action Indicated -- Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and

   c. OAI - Official Action Indicated – Regulatory and/or administrative actions will be recommended.

4. Administrative/Civil/Criminal Actions will be in accordance with 21 CFR Part 361.1. FDA can invoke other legal sanctions under the FD&C Act and/or Title 18, USC, where appropriate.

   a. Administrative Actions for noncompliance -- If apparent noncompliance with FDA regulations (21 CFR 361.1), the FDA can move forward with the following regulatory actions:

- Untitled Letters
- Warning Letters
- Reinspection to verify corrective actions
- Regulatory meetings
- Referral of pertinent matters, with headquarters concurrence, to other Federal, State, or local agencies for such action as that agency deems appropriate

b. **Withdrawal** of FDA Approval

Approval of an RDRC may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section as required by 21 CFR 361.1(c)(4).

5. Communications

The District should promptly inform Headquarters/Centers about any written or oral communication from the institution following the inspection. Similarly, Headquarters/Centers should promptly inform the District of communication (including any written correspondence) with the institution following the inspection, including any judicial/administrative actions. Copies of any written communications should be shared.

B. REGUATORY GUIDANCE

The following criteria are relevant to FDA's classification of inspections of RDRCs:

1. No Action Indicated (NAI)

No objectionable conditions or practices were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action.

Any post-inspectional correspondence acknowledges the RDRC's basic compliance with pertinent regulations.

2. Voluntary Action Indicated (VAI)

Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further regulatory (advisory, administrative, or judicial) action because the objectionable conditions do not meet the threshold for regulatory action (i.e., regulatory violations uncovered during the inspection are few and do not seriously impact subject safety or data integrity).

Post-inspectional correspondence may identify the issues and, when needed, state

that FDA expects prompt, voluntary corrective action by the RDRC.

3. Official Action Indicated (OAI)

   An OAI recommendation is appropriate when regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violations(s) support a finding that:

   Subjects participating in studies approved by the RDRC would be or have been exposed to an unreasonable and significant risk of illness or injury; or

   Subjects' rights would be or have been seriously compromised; or

   Data integrity or reliability is or has been compromised.

   Once an OAI decision is reached, additional information (e.g., previous inspectional findings, correspondence, or other information about the RDRC) may assist the Center in determining the type of post-inspectional correspondence that is appropriate. If the Center chooses to issue a Warning Letter and allow the RDRC to submit a detailed corrective action plan or alternate approach that is acceptable to FDA, the Center should nevertheless be prepared to withdraw approval of the RDRC should the RDRC not respond appropriately (i.e., fails to respond, fails to develop an adequate corrective action plan, or is found, during a subsequent inspection, to have failed to comply with a corrective action plan).

   A Warning Letter may be considered when the violations can be corrected through specific action(s) by the RDRC (e.g., preparation of, and compliance with, a detailed corrective action plan, that is acceptable to FDA) and adherence to the corrective action plan has a high probability of preventing similar or other violations from occurring in the future.

EXAMPLES:

The following are intended to serve as examples of violations that, alone or in combination, would be considered significant and may warrant OAI classification. This list is not all inclusive; other circumstances may also merit OAI classification.

When applying the classification criteria, Center reviewers will generally evaluate the impact of the RDRC's actions (number, scope, and severity of the regulatory violations) on subjects' rights, safety and welfare. There are gradations in the severity of each example, and the specific observation(s) should support the seriousness of the violation(s) and the effect(s) on subjects' safety and welfare and/or the reliability and acceptability of data for FDA decision-making purposes. The Center should also consider whether FDA has cited the RDRC for the same or similar violations during a previous inspection.

TABLE V(B) Inadequate Human Subject Protection

Violation/Related Citation	Examples
Radioactive Drugs for Certain Research Uses 21 CFR 361.1(a)	RDRC has approved studies that do not meet the criteria outlined in the regulation, i.e. basic science research. Study(ies) may require an IND.
Conditions under which use of radioactive drugs for research are considered safe and effective. 21 CFR 361.1(b)(2)	RDRC has approved studies in which there has been no previous experience in humans.
Minutes 21 CFR 361.1(c)(2)	Minutes of RDRC meetings have not been kept.
Approval 21 CFR 361.1(c)(4)	RDRC has failed to inform FDA of changes in membership.
Quality of Radioactive Drug 21 CFR 361.1(d)(6)	RDRC has no mechanism in place to ensure the quality, purity, and sterility of the drug, such as requiring the submission of batch reports.
Adverse Reactions 21 CFR 361.1(d)(8)	RDRC has no mechanism in place to ensure that clinical investigators immediately report all adverse effects associated with the use of the radioactive drug in the research study.
	RDRC has no documentation to support that adverse effects have been reported to FDA.
IRB Approval 21 CFR 361.1(d)(9)	RDRC has no documentation to support that research studies have been approved by an IRB.

C. FOLLOW-UP INSPECTIONS

1. Centers should evaluate whether the violations found indicate systemic problems with the conduct of the study or the reliability of the data and whether additional inspection assignments should be issued (e.g., IRB, clinical investigator(s)).

2. Following issuance of a Warning Letter, Centers should schedule a follow-up inspection to verify if the RDRC is fulfilling the terms of any corrective action plans and is in compliance with applicable regulations. Such follow-up inspections should take place about one year after the date of the last Warning Letter correspondence.

D. POST-INSPECTION INFORMATION SHARING

As per the September 07, 2010, agreement between the Department of Veterans Affairs (VA) and the FDA Office of Regulatory Affairs (ORA) and upon the written request by the Office of Research Oversight, VA, the Center contacts are authorized to provide to the Office of Research Oversight, VA, and its staff, redacted copies of FDA-reviewed EIRs and any post-inspection correspondence issued to VA facilities or employees following any inspection (including the 483s).

Post inspection documents should be sent to:

Chief Officer
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs 810 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

Responses are subject to FDA priority and available resources, and are pursuant to ORA, VA's June 18, 2010, non-disclosure agreement.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. FDA Laws

   Federal Food, Drug, and Cosmetic Act (FD&C Act)

2. Most Relevant 21 CFR Regulations

21 CFR 361.1	Radioactive Drugs for Certain Research Uses
21 CFR 201.129	Labeling – Exemption for Radioactive Drugs for Research Use
21 CFR 312.2(b)(1)	Exemptions for Lawfully Marketed Drugs

3. Other 21 CFR Regulations

Part 11	Electronic Records; Electronic Signatures,

4. FDA Guidelines, Guidances, and Inspection Guides

   - Guidance for Industry: The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM163892.pdf, August 2010)

   - Guidance for Industry: Computerized Systems Used in Clinical Investigations (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf, May 2007)

   - Guidance for Industry: Part 11: Electronic Records, Electronic Signatures-- Scope and Application (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf, August 2003)

   - Guidance for Industry: Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf, Draft October 2010)

   - Investigations Operations Manual (IOM) (http://www.fda.gov/ICECI/Inspections/IOM/default.htm)

   - General Principles of Software Validation; Final Guidance for Industry and FDA Staff (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm, January 2002)

   - Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects –

Supervisory Responsibilities of Investigators
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf, Final October 2009)

B. PROGRAM CONTACTS

1. When medical, technical or scientific questions or issues arise from a specific assignment or if additional information is required about a specific assignment, consult the Center contact identified in the assignment.

2. For operational questions, contact:

   ORA/OMPTO/Division of Medical Products and Tobacco Program Operations
   James Dunnie, Drug Program Expert 301-796-5438, FAX number 301-827-6685
   Ann Marie Montemurro, Director, 301-796-5521, FAX number 301-827-6685

3. For questions about compliance program issues contact:

   Center for Drug Evaluation and Research (CDER)
   Office of Scientific Investigations:
   301-796-3399, FAX 301-847-8748

   Center for Drug Evaluation and Research (CDER)
   Division of Medical Imaging Products
   301-796-2050, FAX 301-796-9849

PART VII - HEADQUARTERS RESPONSIBILITIES

A. Center for Drug Evaluation and Research (CDER):

1. Identify Radioactive Drug Research Committees to be inspected and forward inspection assignments and background material (e.g., annual reports, correspondence, complaints, and Center concerns) to the Director-Investigations Branch, District's BIMO Coordinator, and FACTS.
2. Review and make final classifications of EIRs, and enter the classification into FACTS.
3. Issue correspondence to the inspected institution after EIR review. This letter will typically be addressed to the most responsible individual along with a copy to the RDRC chairperson and will state the Center's assessment of the RDRC's performance. Copies of letters will be sent to the appropriate District Office.
4. Conduct follow-up regulatory and/or administrative actions. Promptly provides copies of relevant correspondence between the institution or RDRC and FDA to the field offices.
5. Provides expert technical guidance, advice, information, interpretation, analysis, and support related to implementation of the clinical BIMO Program for internal and external constituents.

B. DIVISION OF COMPLIANCE POLICY/OE/ORA (HFC-230) *

1. Provides policy and program guidance to agency units who carry out the BIMO Program.
2. Monitors compliance activities to assure uniform application of compliance policy and agency performance in meeting program accomplishment projections for the BIMO Program.
3. Resolves issues involving compliance or enforcement policy.

C. DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS/OE/ORA (HFC-210) *

Serves as the Agency clearance point and coordinator for inspection warrants.

D. DIVISION OF DOMESTIC FIELD INVESTIGATIONS/ORO (HFC-130) *

1. Provides inspection quality assurance, training of field personnel, and operational guidance.
2. Maintains liaison with Centers and Field Offices and resolves operational questions.
3. Coordinates and schedules independent and team inspections.

* Due to 2012 ORA reorganization, division names may have changed.